REMARKS

Status of Claims

Claims 1, 4-9, 12-13, 18-19, and 76-90 are pending after entry of this paper. Claims 2-3, 10-11, 14-17, and 20-75 have been cancelled without prejudice. Applicants reserve the right to pursue cancelled claims in at least one continuing application.

Claim 1 has been amended to include indentations between the different components of the claim for clarity. Claim 1 has also been amended to include the phrase "wherein the microparticulate complex is a precipitate with an average particle size of about 22.5 microns or less." No new matter has been introduced with this amendment. Support can be found throughout the specification as filed, for example on page 43, paragraph [0129] and page 49, paragraphs [0144] and [0147], and Figure 2.

New claims have been added. No new matter has been introduced with these additional claims. Support can be found throughout the specification, claims, and figures as filed, for example:

New Claim 77 finds support on page 43, paragraph [0129] and page 49, paragraphs [0144] and [0147], and Figure 2.

New Claim 78 finds support in claim 1, and on page 43, paragraphs [0128]-[0129] and page 49, paragraphs [0144] and [0147], and Figure 2.

New Claims 79-90 find support in claims 4-9, 12-13, 18-19, and 76, respectively, as well as in claim 1, and on page 43, paragraphs [0128]-[0129] and page 49, paragraphs [0144] and [0147], and Figure 2.

Applicants respectfully request reconsideration and withdrawal of the pending rejections in view of the above-mentioned claim amendment.

Summary Of Interview With The Examiner Pursuant To 37 C.F.R. §1.133

Examiner Le is thanked for her time and discussions during the telephone interview with the applicants' representative, Brandon T. Schurter, on June 23, 2010.

During the interview, applicants' representative discussed the pending claims and references cited in the present Office Action. In particular, applicants' representative discussed how the Morris reference is not in an art analogous to the instant claims and that a person of ordinary skill in the art would not have been motivated to combine Morris with Krieg or Ladd. Applicants' representative also discussed how the instant claims are distinguishable over cited references and further described the difference between the microparticles mentioned in cited references with the microparticulate complex claimed in the present application. Applicants' representative also discussed a proposed amendment with the Examiner. The Examiner indicated that she would need to re-evaluate the claims as a whole in view of the new amendment.

The Examiner also indicated that she would consider new product-by-process claims if they are added to the claim set.

Information Disclosure Statement

The Examiner indicated that several references were not considered on the merits because the IDS allegedly failed to comply with the provisions of 37 CFR 1.97. Applicants respectfully note that the information provided on PTO-1449 appears the same as the information provided by the Examiner in PTO-892 in the related application (Serial No. 10/355,161). Applicants noted that these references were of record in the related application on the Transmittal form filed with the IDS. Applicants resubmit herewith the PTO-1449 form to include the title of the references. Applicants assert that the PTO-1449 form complies with the provisions of 37 CFR 1.97, and respectfully requests that the Examiner consider these references on the merits.

Rejection Under 35 USC § 103(a)

Claims 1, 4-9, 12, 13, 18, 19, and 76 have been rejected under 35 USC 103(a) for allegedly being unpatentable over Krieg in view of Ladd, as evidenced by Morris et al. The Examiner has maintained the rejection over Krieg and Ladd for reasons previously made of record. The Examiner relies on Morris in the present Office Action in rejecting the claims as amended in applicants' last response (Amendment/Response filed March 5, 2010). In particular, new arguments for the 35 USC 103(a) rejection appear on page 7 of the present Office Action. Applicants respectfully disagree with the present rejection.

However, in order to expedite prosecution without disclaimer of, or prejudice to, the subject matter recited in the instant application, applicants have amended independent claim 1 to include the phrase "wherein the microparticulate complex is a precipitate with an average particle size of about 22.5 microns or less." No new matter has been introduced with this amendment. Support can be found throughout the specification as filed, for example on page 43, paragraph [0129] and page 49, paragraphs [0144] and [0147], and in Figure 2.

Applicants incorporate in this response, their prior arguments regarding Krieg and Ladd. Applicants also assert that the new Morris reference does not remedy the deficiencies of Krieg or Ladd. Applicants assert that the instant claims are novel and non-obvious over the cited references (Krieg, Ladd, and/or Morris) when applied alone or in combination for at least the reasons set forth below:

Microparticulate complex is a precipitate

The instant claims are directed to an immunostimulatory microparticulate complex. The immunostimulatory microparticulate complex is a "fine precipitate suspended in solution". (Page 43, paragraph [0129] as filed) (emphasis added).

Applicants assert that none of the cited references teach or suggest an immunostimulatory microparticulate complex that is a fine precipitate in solution. The

microparticles described in Ladd and Krieg are **not** fine precipitates suspended in solution as required by the instant claims. Instead, at best, Ladd and Krieg describe microspheres made of polymers which entrap an immunogen.

For example, Ladd describes in the Summary of the Invention that one approach for delivering immunogens is through "entrapment of immunogen in microparticles. For example, the absorbable suture material poly(lactide-co-glycolide) co-polymer can be fashioned into microparticles containing immunogen" (page 20, lines 33-36) (emphasis added). Ladd further states that "synthetic peptide HLRH immunogens can be improved by delivery through entrapment in or on biodegradable microparticles of the type described by O'Hagan et al." (page 30, lines 14-17) (emphasis added). Additionally, Example 16 of Ladd describes "[m]icroparticles containing peptide A [that] were prepared with a poly(lactide-co-glycolide) copolymer..." (page 69, lines 8-10) (emphasis added). Thus, Ladd does **not** teach or suggest an immunostimulatory microparticulate complex that is a precipitate.

Also, Krieg describes that in a "preferred embodiment the sustained release device is a biodegradable polymer. In another embodiment the sustained release device is a microparticle" (page 10, lines 12-14) (emphasis added). Furthermore, Krieg indicates that in some "embodiments the sustained release device is a micorparticle. In other embodiments the composition includes an antigen" (page 22, lines 1-2 and claims 104 and 105). This further indicates that (1) the microparticle described by Krieg is a microsphere or polymer which entraps the nucleic acid and (2) the microparticle is not a fine precipitate suspended in solution. Finally, Krieg describes microspheres (e.g., page 119, lines 4-5) and microcapsules (e.g., page 120, line 20) which are also not precipitates. Thus, Krieg does **not** teach or suggest an immunostimulatory microparticulate complex that is a precipitate.

Morris describes that since "a larger number of MPG peptides than that theoretically required for charge neutralisation of bound DNA molecules was actually involved in the formation of the MPG/DNA complexes, [they] hypothesised that additional interactions might

take place between peptides, which, as such, most likely formed a 'cage' around the molecule of DNA." (paragraph bridging pages 3512-3513; see also "Conclusions" on page 3516) (emphasis added). Morris mentions, but does not provide any support for, preliminary experiments which allegedly indicate the "existence of particles of MPG/DNA with an average diameter of 200-300 nm" (third full paragraph page 3513). However, Morris does not indicate that these particles are precipitates. Thus, Morris does **not** teach or suggest that the MPG/DNA complexes are precipitates.

Therefore, none of the cited references teach or suggest an immunostimulatory microparticulate complex that is a precipitate.

Precipitate with an average particle size of about 22.5 microns or less

Applicants have amended claim 1 to include the phrase "wherein the microparticulate complex is a precipitate with an average particle size of about 22.5 microns or less." No new matter has been introduced with this amendment. Support can be found throughout the specification as filed, for example on page 43, paragraph [0129] and page 49, paragraphs [0144] and [0147], and in Figure 2.

As discussed above, none of the cited references teach or suggest a microparticulate complex that is a precipitate of any particular size. Thus, applicants assert that none of the cited references teach or suggest a precipitate with an average particle size of about 22.5 microns or less.

Therefore, applicants assert that the instant claims are novel and non-obvious over the references cited by the Examiner in the present Office Action.

A person of ordinary skill in the art would not have been motivated to combine Morris with Krieg or Ladd

Morris describes a technique to enable complete expression of a gene product encoded by a plasmid delivered into a cultured cell. (see Abstract). That is, Morris uses MPG peptide that has a nuclear localization sequence (NLS) to deliver DNA into the nucleus of cultured cells.

A person of ordinary skill in the art would **not have been motivated to combine** Morris with Krieg or Ladd. Specifically, Morris is **not in an art analogous** to Krieg or Ladd. Krieg and Ladd are both directed to immunology and agents which enhance the immune response of an animal, whereas Morris is directed to cell biology, and more specifically to transfection of cells. Applicants assert that a person of ordinary skill in the art would not have been motivated to combine a reference that describes a general transfection technique to overcome or solve problems in the immunology field.

Morris describes using a peptide with an NLS solely to enable DNA to cross the liposomal bilayer membranes and to promote the release of nucleic acids into the nucleus of a cell. Krieg and Ladd, on the other hand, describe enhancing the immune response in an animal through immunostimulatory agents (Krieg) and/or through immunogenic peptides (Ladd). The concepts and inventions described by Krieg and Ladd are not related to or combinable with the technique described by Morris.

Morris would have lead a person of ordinary skill in the art away from the instant claims

Applicants assert that a person of ordinary skill in the art would have been **lead away** from the instant claims if they relied on Morris, because the technique described in Morris would likely destroy any immunogenic response that is desired. Specifically, Morris provides for a technique for transforming a protein/DNA complex into a cell so that the DNA can be expressed. This technique would necessarily result in a protein/DNA complex that would not be available to elicit an efficient immune response.

Specifically, Krieg and Ladd are directed to enhancing an immune response which requires antigen presenting cells (e.g., macrophages and dendritic cells) and/or to other immune cells such as T cells, B cells, and NK cells. (see e.g., Krieg p. 107, lines 14-21; Ladd p. 69, lines 1-7). The transfection technique described by Morris would destroy the intended purpose of Krieg and Ladd, because it would necessarily prevent an antigen from being phagocytosed by cells of the immune system. Moreover, the protein/DNA complex described by Morris would likely enter into a cell that is not even part of the immune system. Thus, a person of ordinary skill in the art would not have been motivated to rely on a reference for transfecting cells for enhancing an immune response, because transfection of the complex would destroy the immunogenic activity of the peptide.

The instant claims are directed to an immunostimulatory microparticulate complex which facilitates the presentation of a peptide immunogen to professional processing cells of the immune system, such as macrophages and dendritic cells. (see e.g., specification p. 43, line 17). Thus, the immunostimulatory complex of the present claims must be presented to immune processing cells in order to be "immunostimulatory". The teachings of Morris would not be compatible with an immunostimulatory complex and, thus, would not be relied on by a person of ordinary skill in immunology. Therefore, applicants assert that combining the teachings of Morris with Krieg or Ladd would have lead a person of ordinary skill in the art away from the instant claims because a combination of these references would destroy the intended immunological purpose of the instant claims.

A transfection charge ratio does not make obvious an immunostimulatory complex charge ratio

The Examiner alleges that the claims presented in the amendment filed March 5, 2010 are obvious over Krieg and Ladd as evidenced by Morris. **However, the Examiner has provided no evidence to show that a charge ratio that is allegedly efficient for shuttling double stranded DNA into the nucleus of a cell is any indication of a charge ratio that**

would be efficient for an immunostimulatory microparticulate complex which elicits an immune response in an animal.

As discussed above, the immunostimulatory complex of the instant claims facilitates the presentation of a peptide immunogen to professional processing cells of the immune system, such as macrophages and dendritic cells. (see e.g., specification p. 43, line 17). That is, the immunostimulatory complex of the present claims must be presented to immune processing cells in order to be "immunostimulatory". The method described by Morris is completely unrelated to presentation of a peptide immunogen to cells of the immune system and, as such, does not teach or provide any guidance regarding what DNA:peptide charge ratio would be appropriate for an immunostimulatory microparticulate complex. Thus, applicants respectfully submit that Morris does not render the instant claims obvious, for the additional reason that Morris provides no guidance for what charge ratio, if any, would be appropriate for an immunostimulatory complex.

Accordingly, none of the cited references alone or in combination provide guidance with regard to a DNA:peptide charge ratio for microparticulate complexes that are, or would be, immunostimulatory. Therefore, applicants assert that the instant claims are novel and non-obvious over the cited references.

Morris would not want to elicit an immune response with its complex

Applicants assert that there would also be no motivation to combine Morris with Krieg and Ladd because Morris contemplates that this method "is of prime interest for the development of new gene therapy strategies." ("Conclusions" page 3516). Thus, it would be detrimental to Morris if an immune response were to be elicited by/against the protein/DNA transfection complex. That is, any gene therapy relying on transfection of DNA by a protein/DNA complex would be inefficient if an immune response were to be elicited by/against the complex.

As the Examiner is aware, the Patent Office's Manual of Patent Examining Procedure ("MPEP") explicitly states:

> If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. M.P.E.P. § 2143.01(V) (citing In re Gordon, 733 F.2d 900 (Fed. Cir. 1984)).

Moreover, in In re Gordon the Federal Circuit stated:

> We are persuaded that the board erred in its conclusion of prima facie obviousness. ... The question is ... whether it would have been obvious from a fair reading of the prior art reference as a whole to [make the proposed modification]. ... The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification. In re Gordon, 733 F.2d at 902.

Applicants assert that modifying Morris to be compatible with an immunostimulatory complex would destroy the intended purpose of Morris. Therefore, there would have been no motivation to modify or combine Morris with Krieg and/or Ladd and, applicants respectfully submit, that any attempt to now do so would run counter to USPTO guidelines and CAFC precedent.

Morris is directed to transfecting cells with double-stranded DNA

Applicants assert that there would also have been no motivation to combine Morris with Krieg or Ladd, or to modify Morris to use single-stranded DNA as required by the present claims. Similar to arguments presented above, there is no indication that the double-stranded DNA:peptide charge ratio described by Morris would be appropriate for a single-stranded DNA:peptide of an immunostimulatory complex. Therefore, Morris does not provide a person of ordinary skill in immunology with any guidance with regard to DNA:peptide charge ratios.

Morris does not consider the stability of the complex as a whole

Morris describes that the complex allegedly protects the DNA from degradation (Stability and DNase I protection assays, page 3511). Applicants respectfully point out that the instant

claims are directed to a stabilized complex comprising both the peptide immunogen and the CpG oligonucleotide. The instant claims are directed to a stabilized complex comprising a single-stranded oligonucleotide and a peptide. Morris, on the other hand, does not consider the stability of the peptide, or the complex as a whole.

Improper Hindsight Reconstruction

In view of at least the reasons discussed above, it appears that the Examiner improperly relied on **hindsight reconstruction** to reject the claims over the cited references. That is, the Examiner has relied on the teachings of the instant application in order to pick and choose elements from the cited references to allegedly reconstruct the instant claims. In doing so, the Examiner has taken the teachings of the cited references out of context in order to fit the rejection/argument.

As discussed above, applicants assert that a person of ordinary skill in the art would not have been motivated to rely on Morris, let alone combine Morris with Krieg or Ladd, because (1) Morris is directed to transfecting cells, which is unrelated to immunology; (2) the technique described by Morris (i.e., shuttling a protein:DNA complex into the nucleus of a cell) is incompatible with the purpose of the present invention (i.e., presenting an immunogen to the cells of the immune system); (3) there is no indication that a charge ratio that is allegedly efficient for transfecting cells would also be efficient for eliciting an immune response; and (4) the goal/purpose of Morris would be destroyed if the protein:DNA complex were to elicit an immune response.

Accordingly, applicants respectfully submit that the combination of Morris with Krieg and Ladd proposed in the Office Action is based solely on the teachings of the present application.

Conclusion

Applicants assert that the instant claims are novel and non-obvious. The cited references, alone or in combination, do not teach or suggest each and every element of the instant claims. Accordingly, applicants respectfully request reconsideration and withdrawal of the rejection to the pending claims in view of the above-mentioned amendments and remarks.

New Claims

Applicants have included several new claims as suggested/recommended by the Examiner during the telephone interview on June 23, 2010. Applicants assert that the composition claims (i.e., Claims 1, 4-9, 12-13, 18-19, and 76) are novel, non-obvious, and patentable for at least the reasons set forth above. Applicants present new product-by-process claims in order to further prosecution and to include additional claims in the present application. Applicants expressly assert that including product-by-process claims in the present claim set **does not indicate or imply** any admission that the composition claims are in any way unpatentable.

The new claims are directed to a composition (i.e., immunostimulatory microparticulate complex) that is formed by combining the CpG oligonucleotide to the cationic peptide immunogen, or vice versa, in a dropwise manner to form a precipitate with an average particle size of about 22.5 microns or less. Support can be found throughout the specification and claims as filed, for example in claims 1, 4-9, 12-13, 18-19, and 76 as well as and paragraphs [0128]-[0147] on pages 43-49 and in Figure 2 of the application as filed. Applicants note that the "Preparation of Immunostimulatory Complex" section on pages 43-45, Example 1 on pages 45-49, and Figure 2 provide explicit written support for an immunostimulatory microparticulate complex that is formed by combining the CpG oligonucleotide and the peptide together in a dropwise manner. Additionally, Figure 2 illustrates that the average particle size of the

immunostimulatory microparticulate complex is about 22.5 microns or less between the claimed charge ratio range of 8:1 to 1:2.

Applicants respectfully request entry and allowance of the new claims in view of the above mentioned remarks.

Dependent Claims

Applicant has not independently addressed all of the rejections of the dependent claims. The applicant submits that for at least similar reasons as to why independent claims, from which all of the dependent claims depend, are allowable as discussed above, the dependent claims are also allowable. Applicant, however, reserves the right to address any individual rejections of the dependent claims and present independent bases for allowance for the dependent claims should such be necessary or appropriate.

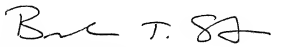
CONCLUSION

Based on the foregoing amendments and remarks, applicant respectfully requests reconsideration and withdrawal of the rejection of claims and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **504827**, Order No. 1004263.156US.

Respectfully submitted,
LOCKE LORD BISSELL & LIDDELL LLP

By: 

Brandon T. Schurter
Registration No. 59,668

Dated: June 25, 2010

Correspondence Address:
Address Associated With Customer Number:
85775

(212) 415-8600 Telephone
(212) 303-2754 Facsimile